assay (either of brain NP [BNP] or of the *N*-terminal fragment of BNP [NT-proBNP]) in complex congenital defects (congenital heart disease [CHD]). Their literature review is mostly focused on the applications of NPs for the follow-up of some CHD (1). However, we would like to remind that NPs may be also used for neonatal screening purposes (2,3), differential diagnosis, prognostic stratification (in children undergoing cardiac surgery) (2,4), and to guide the surgical/medical management of CHD, including complex defects (2), as it is the case for the setting of heart failure (5).

Moreover, variability associated with both physiological and methodological sources is a relevant issue to be taken into account for proper clinical use of NPs in patients of pediatric age.

In particular, NP levels in healthy subjects are very high during the first 4 days of life, while decreasing thereafter, rapidly throughout the first week, with a further slow progressive reduction for up to the first month of life (6). After the first month of life, NPs show no more significant age- or gender-related differences up to puberty (2,6).

Furthermore, the measured NP concentrations, as well as reference ranges and decisional cutoff values, are strictly method dependent (5). The diagnostic accuracy of NPs in neonates with CHD, too, varies up to the first month of life, with low levels in the first 3 days after birth (2). These findings are likely due to the different timecourse of NP levels observed either in healthy neonates or in newborns with CHD. In the first 3 days of life, BNP levels are very high in both healthy subjects and patients, whereas after the fourth day peptide levels rapidly and progressively fall only in healthy neonates. For these reasons, we have suggested two different cutoff values to rule in or out CHD: the first, characterized by higher values from 1 to 3 days of life; and the second with lower values from days 4 to 30 of life (2). Furthermore, because various methods have been employed by different authors (1,2), the influence of the analytical contribution to BNP/NT-proBNP concentration variability, by the assay method, needs to be evaluated (2).

In conclusion, the assay of NPs may be considered as helpful for screening, diagnostic, prognostic, and follow-up purposes, to be included into an integrated approach to children with suspected or ascertained complex CHD. Nevertheless, biological (age-related) and method-related variability needs to be taken into account when interpreting NP values in this setting, especially in the neonatal age.

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REFERENCES

1. Eindhoven JA, van den Bosch AE, Jansen PR, Boersma E, Ross-Hesselink JW. The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review. J Am Coll Cardiol 2012;60:2140–9.
2. Cantinotti M, Giovannini S, Murzi B, Clerico A. Diagnostic, prognostic and therapeutic relevance of B-type natriuretic hormone and related peptides in children with congenital heart diseases. Clin Chem Lab Med 2011;49:567–80.
3. Law YM, Hoyer AW, Reller MD, Silberbach M. Accuracy of plasma B-type natriuretic peptide to diagnose significant cardiovascular disease in children: the Better Not Pout Children! study. J Am Coll Cardiol 2009;54:1467–75.
4. Niedner MF, Foley JL, Riffenburgh RH, Bichell DP, Peterson BM, Rodarte A. B-type natriuretic peptide: perioperative patterns in congenital heart disease. Congenit Heart Dis 2010;5:243–55.
5. Clerico A, Emdin M. Diagnostic accuracy and prognostic relevance of the measurement of cardiac natriuretic peptides: a review. Clin Chem 2004;50:33–50.
6. Cantinotti M, Storti S, Parri MS, Murzi M, Clerico A. Reference values for plasma BNP circulating levels in the first days of life. Clin Chem 2009;55:1438–40.

Reply

We thank Dr. Cantinotti and colleagues for their interest in our article (1) and for their valuable addition. We fully agree with Cantinotti et al. that brain natriuretic peptides (NPs) are of potential use for other purposes as differential diagnosis and to guide medical and surgical management of congenital heart disease (CHD). In our systematic review we aimed to provide a clear overview of average NP levels for the 3 most commonly encountered complex congenital heart defects and the relation with cardiac function to determine its possible use in the cardiologists' daily practice. The use of this biomarker at young pediatric age is so far mainly studied in mixed cohorts of various forms of CHD (2). As we looked at disease-specific NP values, these studies were not included in our review article. Nevertheless, daily changes in BNP in the first days of life and suggested cutoff values for NPs in this period clearly provide valuable diagnostic information for both neonatologists and pediatric cardiologists.

Cantinotti et al. also note that the various assay methods used to determine NP levels measure different NP concentrations and have assay method–specific cutoff values (3). We acknowledge this fact, and it was our main reason to withhold us from a direct comparison of the observed NP values by performing a formal meta-analysis. By reporting both NP values for CHD patients and, when reported, NP values for healthy controls per study (Figure 2 [1]), we aimed to demonstrate the observed differences objectively without drawing any overall conclusions. Despite known differences between assay kits, the measured NP levels and observed correlations were comparable, strengthening the potential clinical use of NPs in CHD (1). Furthermore, the additional prognostic value of the marker remains to be clarified by larger longitudinal studies.

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REFERENCES

1. Eindhoven JA, van den Bosch AE, Jansen PR, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review. J Am Coll Cardiol 2012;60:2140–9.
2. Johns MC, Stephenson C. Amino-terminal pro-B-type natriuretic peptide testing in neonatal and pediatric patients. Am J Cardiol 2008;101:76–81.
3. Clerico A, Emdin M. Diagnostic accuracy and prognostic relevance of the measurement of cardiac natriuretic peptides: a review. Clin Chem 2004;50:33–50.

Appropriate Use Criteria to Reduce Underuse and Overuse of Revascularization

Although the appropriate use criteria (AUC) for the performance of revascularization are well meaning, important limitations include the facts that they: 1) represent the consensus of a limited group of stakeholders; 2) classify a minority of possible permutations of patient scenarios; 3) do not incorporate essential data points, including specific lesion characteristics, extent of myocardium supplied, fractional flow reserve and intravascular ultrasound data, and important comorbidities (diabetes mellitus, chronic kidney disease, and so forth); 4) are based on data recording in the National Cardiovascular Data Registry by persons with widely variable training and motivation without systematic monitoring, adjudication, or audit; 5) undervalue quality of life issues, and in this regard, ignore patient preferences; and 6) do not emphasize underuse of percutaneous coronary intervention (1–4).

In this regard, Ko et al. (5) report that almost one-third of subjects undergoing angiography in Ontario, Canada, between April 2006 and March 2007 deemed "appropriate" by U.S. AUC criteria were not revascularized. Such patients experienced appreciably worse clinical outcomes (increased incidence of death or acute coronary syndrome presentation) through 3-year follow-up (hazard ratio [HR] of revascularization vs. medical therapy: 0.61; 95% confidence interval [CI]: 0.42 to 0.88). In the accompanying editorial, Patel (6) states: "This reduction in clinical events was not seen in patients with a revascularization classification (appropriateness score) of uncertain (HR: 0.57; 95% CI: 0.28 to 1.16) or inappropriate (HR: 0.99; 95% CI: 0.48 to 2.02)" (6).

Although we agree with Dr. Patel regarding the apparent lack of benefit associated with revascularization (vs. medical therapy) in subjects scored as inappropriate (at least as regards death or new acute coronary syndrome, although chronic angina and quality of life data were not collected), we disagree with the conclusion for the "uncertain" patients. Given the point estimate and confidence interval, this may well represent type II error. As evident from the nearly identical HRs, the magnitude of benefit provided by revascularization (vs. medical therapy) may be at least as great among the "uncertain" and "appropriate" classified cohorts, but was obscured by the relative lack of power (only 326 subjects classified as uncertain vs. 991 subjects classified as appropriate). Upsizing the uncertain cohort to 991 subjects, with proportionally similar event rates for revascularized (8%; 43 events) and medically treated (15.3%; 70 events) subjects, results in an odds ratio for revascularization (vs. medical therapy) of 0.48 (95% CI: 0.31 to 0.73), a highly statistically significant difference. Thus, on the basis of this report, larger studies are warranted to determine whether the spectrum of patients benefitting from revascularization should expand to include the uncertain group (which would further enlarge the specter of underuse).

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REFERENCES

1. Stone GW, Moses JW. Interventional cardiology: how should the appropriateness of PCI be judged? Nat Rev Cardiol 2011;8:544–6.
2. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA 2009;301:831–41.
3. Chan PS, Brindis RG, Cohen DJ, et al. Concordance of physician ratings with the appropriate use criteria for coronary revascularization. J Am Coll Cardiol 2001;57:1546–53.
4. Marso SP, Teirstein PS, Kereiakes DJ, Moses J, Lasala J, Grantham JA. Percutaneous coronary intervention use in the United States: defining measures of appropriateness. J Am Coll Cardiol Intv 2012;5:229–35.
5. Ko DT, Guo H, Wijeysundera HC, et al., for the Cardiac Care Network (CCN) of Ontario Variations in Revascularization Practice in Ontario (VRPO) Working Group. Assessing the association of appropriateness of coronary revascularization and clinical outcomes for patients with stable coronary artery disease. J Am Coll Cardiol 2012;60:1876–84.
6. Patel MR. Appropriate use criteria to reduce underuse and overuse: striking the right balance. J Am Coll Cardiol 2012;60:1885–7.

Reply

We appreciate the insightful comments provided by Drs. Kereiakes and Stone on our study (1). Applying the appropriate use criteria of coronary revascularization on patients with stable coronary artery disease afforded new insights on the potential overutilization, underutilization, and uncertain use of coronary revascularization in contemporary practice (2). In our population-based cohort assembled in Ontario, Canada, we observed the majority (68%) of coronary revascularizations were considered appropriate, 18% were considered uncertain, and 14% were considered inappropriate. Among patients who had appropriate indications, we found that coronary revascularization was associated with a 39% lower hazard of adjusted death or repeat acute coronary syndrome at 3 years. We also observed that 31% of patients in the appropriate category did not receive revascularization, suggesting that underutilization of therapy is still prevalent in clinical practice. In contrast, patients who had inappropriate indications and received coronary revascularization or medical therapy had no significant difference in hazard of death or acute coronary syndrome, suggesting potential overutilization of coronary revascularization in this subgroup. Finally, many clinical scenarios in the appropriateness